Introduction and objectives

Cytochrome P450 (CYP) enzymes are prominent xenobiotic metabolism enzymes that detoxify or activate xenobiotic compounds. The CYP1A2 enzyme is involved in the metabolism of about 9% of marketed drugs [1]. Cigarette smoking, through exposure to polycyclic aromatic hydrocarbons (PAHs), has been shown to induce CYP1A2 enzyme activity [2], and its levels are elevated in xenobiotic-exposed smokers compared to non-smokers [3]. Sudden smoking cessation and the subsequent abolishment of CYP1A2 induction has been documented in numerous case reports to be associated with adverse drug reactions [4].

Philip Morris International (PMI) has developed a range of Reduced-Risk Products (RRP) that are present, are likely to present, and have the potential to present less risk of harm to human adults who switch to these products versus continuing smoking. One of these products is the Tobacco Heating System (THS 2.2, currently marketed in numerous countries under the brand name iQOS® with HEETS®, a candidate Modulator of Risk Tobacco Product (MRTP) for which PMI has implemented an assessment program that follows the U.S. Food and Drug Administration MRTP Applications Draft Guidance [5].

PMI assessment studies have evaluated CYP1A2 gene and protein expression in animal models, CYP1A1/1B1 activity in human organotypic cultures, and CYP1A2 activity in humans. Harmful and potentially harmful constituents (PHHC) of cigarette smoke (CS), including PAHs, are reduced by 90%–95%, on average, in THS 2.2 aerosol compared with CS from a standard 3R4F reference cigarette [6].

Here, we assess to what extent the lower PHHC levels in THS 2.2 aerosol, compared with CS, are associated with a lower exposure to xenobiotic processes, especially CYP1A2, upon exposure in pre-clinical and clinical studies carried out by PMI.

Methods

The pre-clinical exposure studies evaluated protein and mRNA expression changes for CYP1A2 in liver for two ApoE-/- mouse studies [7,14]. Female ApoE-/- mice were exposed for up to six or eight months to fresh air (Sham), 3R4F CS, or THS 2.2 aerosol at matched nicotine concentrations. Human organotypic nasal cultures were exposed to fresh air (Sham), 3R4F CS, or THS 2.2 aerosol at the air-water interface [13]. Controlled-applied CYP1A1/1B1 activity was measured using a non-tryp 50GlsH® assay (Promega, Madison, WI, USA).

The clinical studies included two five-day [8,9] and two 90-day reduced exposure studies [10-12]:

• The five-day studies described the changes in CYP1A2 enzymatic activity on Day 5 in smokers i) switching from regular cigarettes to THS 2.2 with regular (non-methyl) heatsticks, ii) continuing to smoke regular cigarettes, and iii) smoking abstinence (SA).

• The 90-day studies described the change in CYP1A2 enzymatic activity (on Days 5 & 90) in smokers i) switching from mentholated cigarettes to THS 2.2 with menthol heatsticks (M); ii) continuing mentholated cigarette smoking, and iii) SA. The results presented refer to the par protocol (PP) populations.

• The measurement of enzyme activity was assessed through paranthamine and caffeine (CAF) plasma molecular concentrations approximately six hours (±15 minutes) after the intake of either one cup of coffee made from 4.2 (± 0.5 g) instant coffee Nissum Gold Instant; Nestle; Germany; CAF content: 72 mg/g) with 150 ml of milk or one Tomumir® CAF tablet with 150 ml of milk.

Results

• Compared to Sham exposure, elevated levels of CYP1A2 were observed in the livers of ApoE-/- mice exposed to CS from the 3R4F reference cigarette but not in mice exposed to THS 2.2 aerosol at matching nicotine concentrations (Table 1). Upon both cessation and switching to THS 2.2, the upregulation of CYP1A2 observed upon CS exposure reverted to levels close to Sham.

• A causal biological network model that captures the xenobiotic network response demonstrated weaker perturbation upon THS 2.2 exposure compared with CS exposure in the lung of ApoE-/- mice (Figure 1).

• The combined enzymatic activity of CYP1A1/1B1 was lower in human organotypic nasal cultures exposed to THS 2.2 aerosol than those exposed to 3R4F CS (Figure 2).

• In four clinical studies conducted with THS 2.2, CYP1A2 activity was lower in the plasma of subjects who abstained from smoking or switched to THS 2.2 for five days compared with subjects who continued smoking (Table 2 and Figure 3).

Discussion

In the pre-clinical studies, exposure to THS 2.2 aerosol did not result in significant differential expression of CYP1A2 in liver tissue [13]. Mice, exposed the xenobiotic response in the lung to a much lower extent (13%). In the 3R4F CS, and was associated with lower activity of CYP1A1/1B1 compared to human organotypic cultures. The clinical studies assessing CYP1A2 enzymatic activity in smokers switching to THS 2.2 and after smoking cessation showed reductions in CYP1A2 in switches to THS 2.2 comparable to those seen in those who quit smoking.

Smoking of 10–20 cigarettes per day appears to be a weak to moderate inducer of CYP1A2, depending on the contribution ratio value for CYP1A2 (CYP1A1/1B1) of the metabolite drug. In smokers, drugs that are primarily metabolized by CYP1A2 will have faster systemic clearance as a result of enzyme induction [2].

On the other hand, there is substantial evidence showing that smoking cessation results in downregulation of the CYP1A2 enzymatic activity [26]. It has been shown to reverse induced hepatic enzyme levels to normal [9]. After sudden smoking cessation, initial CAF clearance decreased, and the apparent half-life of CYP1A2 activity was 38.6 hours (20-44.4 hours). Therefore, after smoking cessation, there might be a need for dose adjustment of drugs metabolized by CYP1A2.

Data from case reports of smokers switching to e-cigarettes use have shown a similar decrease in CYP1A2 activity. There are multiple cases of elevations of CYP1A2 metabolized drug levels in those who stopped smoking, in particular those in who were taking Clozapine. The same was observed in those who switched to e-cigarettes.

Nicotine replacement therapy to assist smoking cessation will not improve this effect, because the effect on hepatic enzymes is related to nicotine but not to NRTs.

Even though current cessation guidelines do not mention the need to adjust the dosage of CYP1A2 metabolized drugs after smoking cessation, this is recommended in clinical practice, especially for drugs with a narrow therapeutic index. Particularly, increased plasma concentrations of these drugs after smoking cessation may cause serious clinical consequences [16]. Due to the short turnover time of CYP1A2, empirical dose reduction may be necessary within two to three days after smoking cessation.

Because both CYP1A2 expression and activity reductions have been shown to be comparable in quitters and those switching to THS 2.2 due to reduction in exposure to PAHs [8], the same recommendations for dose adjustment for CYP1A2 metabolized drugs that guarantee a reduction in the exposure to PAHs should be made upon switching to RRPs.

Conclusions

Taken together, these results demonstrate an overall reduced impact on xenobiotic metabolism upon exposure to THS 2.2 aerosol compared with CS in non-clinical in vitro and in vivo studies as well as clinical studies.

Switching to RRPs reduces CYP1A2 activity to a similar extent as smoking cessation. The same recommendations for dose modification made for smokers upon cessation should be extrapolated to smokers switching to THS 2.2 or other RRPs.

End-users and quitters should be made aware of any unwanted effects associated with smoking cessation that might affect a smoker’s ability to quit as well as the potential effects of switching to RRPs.

References